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Efficacy, acceptability and tolerability of the combined contraceptive ring, NuvaRing, compared with an oral contraceptive containing 30 μg of ethinyl estradiol and 3 mg of drospirenone

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Abstract

Purpose: This randomized multicenter, open-label, trial compared efficacy, acceptability, tolerability and compliance of NuvaRing with a combined oral contraceptive (COC), containing 30 μg of ethinyl estradiol (EE) and 3 mg of drospirenone.
Method: In this 13-cycle study, 983 women were randomized and treated (intent-to-treat population) with NuvaRing or COC.
Results: One in-treatment pregnancy occurred with NuvaRing (Pearl Index=0.25) (95% confidence interval [CI]: 0.006, 1.363) and four with the COC (Pearl Index=0.99) (95% CI: 0.269, 2.530). For both groups, compliance (89.2% NuvaRing, 85.5% COC) and satisfaction (84% NuvaRing; 87% COC) were high; the vast majority of women found NuvaRing easy to insert (96%) and remove (97%). Tolerability was similar; the most frequent adverse events with NuvaRing were related to ring use, whereas estrogen-related events were more common with the COC.
Conclusion: NuvaRing has comparable efficacy and tolerability to a COC containing 30 μg of EE and 3 mg drospirenone. User acceptability of both methods was high.

Keywords: NuvaRing; Contraceptive; Compliance; Efficacy; Tolerability; Pill

1. Introduction

Combined oral contraceptives (COCs) are an effective and well-established method of contraception. However, contraceptive pills are associated with a number of potential disadvantages, the most important one being the requirement for daily administration. In addition, fluctuations in plasma contraceptive hormone concentrations, hepatic first-pass metabolism and potential gastrointestinal interference with absorption may occur [1–4].

Research into alternative methods of contraception that avoid daily administration has resulted in the development of the monthly combined contraceptive ring (NuvaRing®, Organon, Oss, The Netherlands). The NuvaRing is a flexible ring which releases 15 μg of ethinyl estradiol (EE) and 120 μg of etonogestrel per day over 3 consecutive weeks. The ring can be easily self-inserted and removed.

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The advantages of NuvaRing include the use of lower doses of contraceptive hormones [5] and its controlled-release delivery that avoids daily fluctuations in hormone levels. The excellent efficacy, tolerability and acceptability of NuvaRing have been established in large-scale studies conducted in Europe and North America [6–8]. Furthermore, the contraceptive efficacy and tolerability of NuvaRing have recently been shown to be equal to that of a COC containing 30 μg of EE and 150 μg of levonorgestrel [8,9].

The aim of the present study was to compare NuvaRing's efficacy, acceptability and tolerability with that of a commonly used COC containing 30 μg of EE and 3 mg of drospirenone (Yasmin®, Schering, Berlin, Germany). In addition, patient compliance with these two forms of contraception was assessed. A comparison of the effects of these two contraceptives on cycle control and body weight will be discussed in a separate article.

2. Subjects and methods

This was a randomized, open-label, multicenter trial which was conducted between May 2002 and April 2004. Subjects were recruited from gynecological and/or general practitioner's practices in 10 European countries (Austria, Belgium, Denmark, France, Germany, Italy, Norway, Spain, Sweden and Switzerland). All subjects provided written informed consent. The trial was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonisation Guideline for Good Clinical Practice and was approved by the independent ethics committee/institutional review boards of the participating centers.

2.1. Subjects

The study recruited women (≥18 years at screening) at risk of pregnancy and seeking contraception. Key exclusion criteria included the following: contraindications for contraceptive steroids, abortion or breastfeeding within 2 months before the start of study treatment, injectable hormonal contraceptive use within 6 months of the start of the trial, abnormal cervical smear diagnosed during screening and current use or use within 2 months of drugs that interfere with the metabolism of contraceptive hormones.

2.2. Study treatments

Subjects received treatment for 13 consecutive cycles. The duration of each cycle was 28 days, comprising a 21-day ring/pill treatment period followed by a 7-day ring- or pill-free period. Women were randomized 1:1 to the two treatment groups (NuvaRing and COC) using an Interactive Voice Response System.

2.2.1. Ring use

Subjects received instruction on ring use on entry to the study, including how and when to insert and remove NuvaRing. Women who were taking no hormonal contraception inserted the ring between Days 1 and 5 of the menstrual cycle according to the instructions in the package insert. Women using other methods of contraception followed the instructions in the package insert, according to their method of use.

2.2.2. Pill intake

Women with no preceding hormonal contraceptive use in the past month started pill taking on the first day of menstrual bleeding. Women using other methods of contraception followed the instructions in the package insert, according to the method they were using. It should be noted that based upon the instructions in the package inserts, the study protocol did not include a Sunday start for pill intake.

2.3. Study assessments

Assessments were performed at screening (within 1 month before commencing treatment) and/or within 1 week after the ring-/pill-free period of cycles 1, 3, 6, 9 and 13 (or at premature discontinuation from the study).

2.3.1. Contraceptive efficacy

The contraceptive efficacy of NuvaRing and the COC was determined by the occurrence of pregnancy during the study. A home pregnancy test was carried out just prior to commencing study medication and at any point during the study if pregnancy was suspected (or whenever required by local Drug Laws). At the end of the last treatment cycle (cycle 13 or premature discontinuation), pregnancy status was assessed by measuring serum β-human chorionic gonadotrophin. Any pregnancy occurring during the study was fully documented.

2.3.2. Compliance

Diary cards were used to record ring/pill use, and these data were used to determine exposure and dosing compliance. In the COC group, full compliance was defined as a cycle in which all scheduled pills were taken. For NuvaRing, a cycle was considered compliant if the period of ring use did not deviate by >48 h from the scheduled 3 weeks and the ring-free period did not deviate by >24 h from the scheduled 1 week.

2.3.3. User acceptability

User acceptability was assessed using a questionnaire that was completed by the subject after cycles 1, 3, 6, 9 and at the end of the trial (after cycle 13 or at early discontinuation). At screening, a reduced number of questions from the user acceptability questionnaire were asked, as most questions in the questionnaire were not applicable at trial start.

2.3.4. Tolerability

For all subjects, a general medical and gynecological history was provided at screening, and all subjects underwent physical and gynecological examinations, including a cervi-

cal smear test if needed (a cervical smear <1 year before screening could be used for this assessment). At all study visits, body weight and blood pressure were recorded. Body mass index was calculated at enrolment. Adverse event data and concomitant medication use were recorded throughout the trial. At the last study visit, physical examination and a cervical cytology assessment were repeated.

2.4. Statistical methods

The all-subjects-treated (AST) group comprised all subjects who received at least one pill/ring. The intent-to-treat (ITT) group consisted of all randomized subjects from the AST group. The per-protocol (PP) group consisted of all subjects from the ITT group without any major protocol

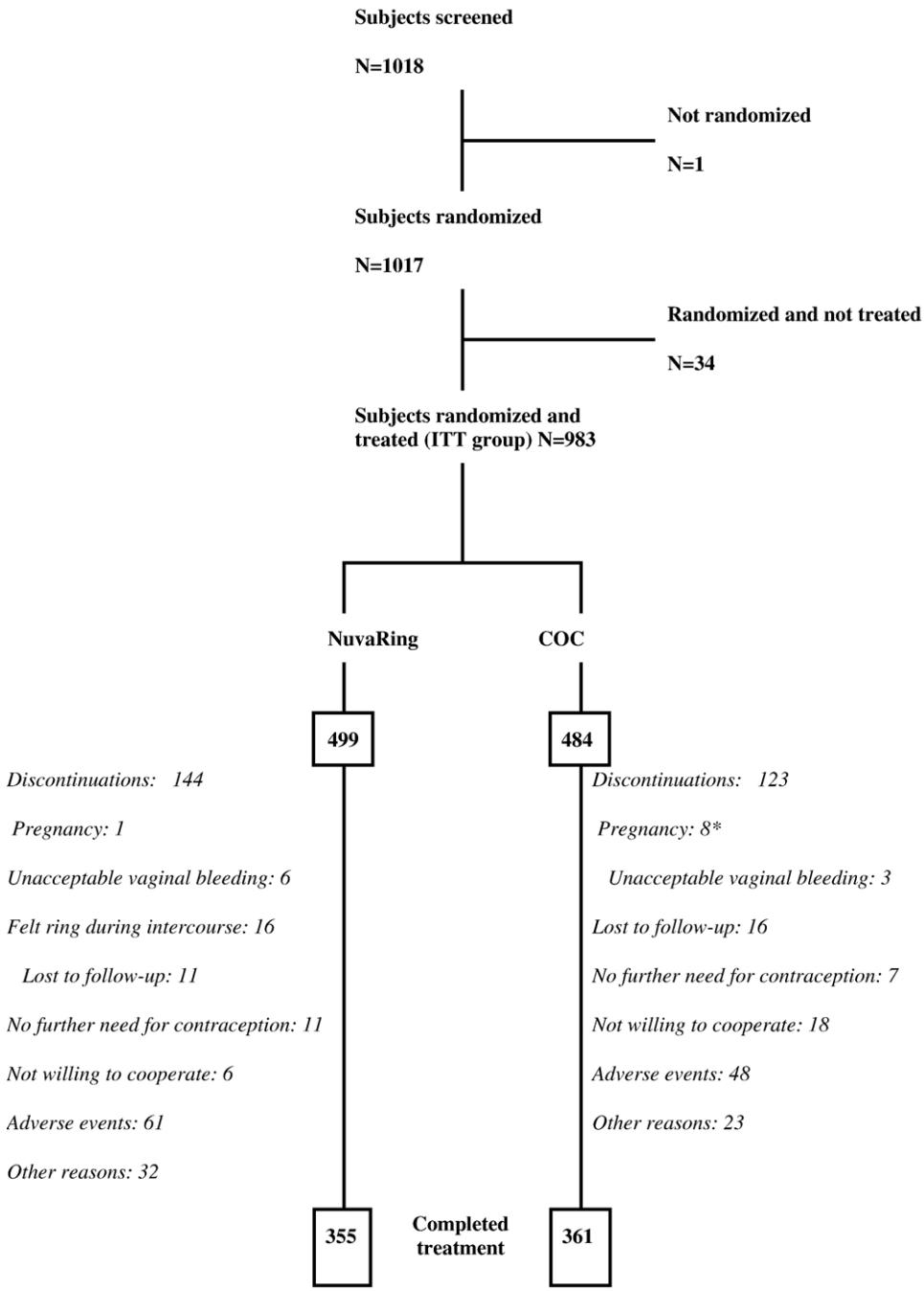

Fig. 1. Subject disposition.

violation. Discontinuation rates were compared by means of the Kaplan-Meier method and the log-rank test.

The Pearl Index (expected number of in-treatment pregnancies/100 women-years of exposure) and its 95% confidence intervals (CIs) were used to estimate contraceptive efficacy. CIs were calculated by assuming an underlying Poisson distribution.

Tolerability was analyzed for the AST population using descriptive statistics. User acceptability was evaluated using frequency tables (of answers from subject questionnaires) for the AST group.

3. Results

3.1. Subjects

3.1.1. Disposition

A total of 1017 women were randomized. Of these, 34 discontinued before receiving treatment for the following reasons: 7 (NuvaRing, $n=4$; COC, $n=3$) were pregnant at screening; 10 (NuvaRing, $n=6$; COC, $n=4$) were not willing to cooperate any further; one (COC) was lost to follow-up; one (NuvaRing) had no further need for contraception and 15 (NuvaRing, $n=6$; COC, $n=9$) discontinued for other reasons (Fig. 1). A total of 983 subjects (NuvaRing, $n=499$; COC, $n=484$) were randomized and treated (ITT group). Of these, 267 subjects (NuvaRing, $n=144$ [28.9%]; COC, $n=123$ [25.4%]) discontinued prematurely, primarily due to adverse events (NuvaRing, $n=61$; COC, $n=48$) and other reasons (NuvaRing, $n=32$; COC, $n=23$); overall, 716 women completed the trial (NuvaRing, $n=355$ [71.1%]; COC, $n=361$ [74.6%]). The initial discontinuation rate in the NuvaRing group was higher than in the COC group (Fig. 2), but the overall discontinuation rate was not significantly different between treatment groups (log-rank test: p=.208).

3.1.2. Baseline characteristics

There were no notable differences between the two groups in baseline demographic or clinical characteristics (Table 1). The most frequently used contraceptive method prior to enrolment in both groups was COCs (NuvaRing 68.5%; COC 66.6%), i.e., a COC containing ≥ 30 μg of EE (50.9% and 49.0%, respectively) or a COC containing 20 μg of EE (17.6% for each group). Foam, condoms, suppositories or diaphragms comprised the next most commonly used group of contraceptive methods (NuvaRing 18.4%; COC 18.8%). The majority of subjects in both groups were satisfied or very satisfied (NuvaRing 62.7%; COC 65.9%) with their previous method of contraception.

3.2. Contraceptive efficacy

A total of five in-treatment pregnancies occurred in the ITT population (NuvaRing $n=1$; COC $n=4$). Of these, the one subject in the NuvaRing group and two in the COC group had no protocol violations. In the two remaining pregnancies, women forgot pills in the cycle preceding conception or in the cycle of conception itself. Treatment

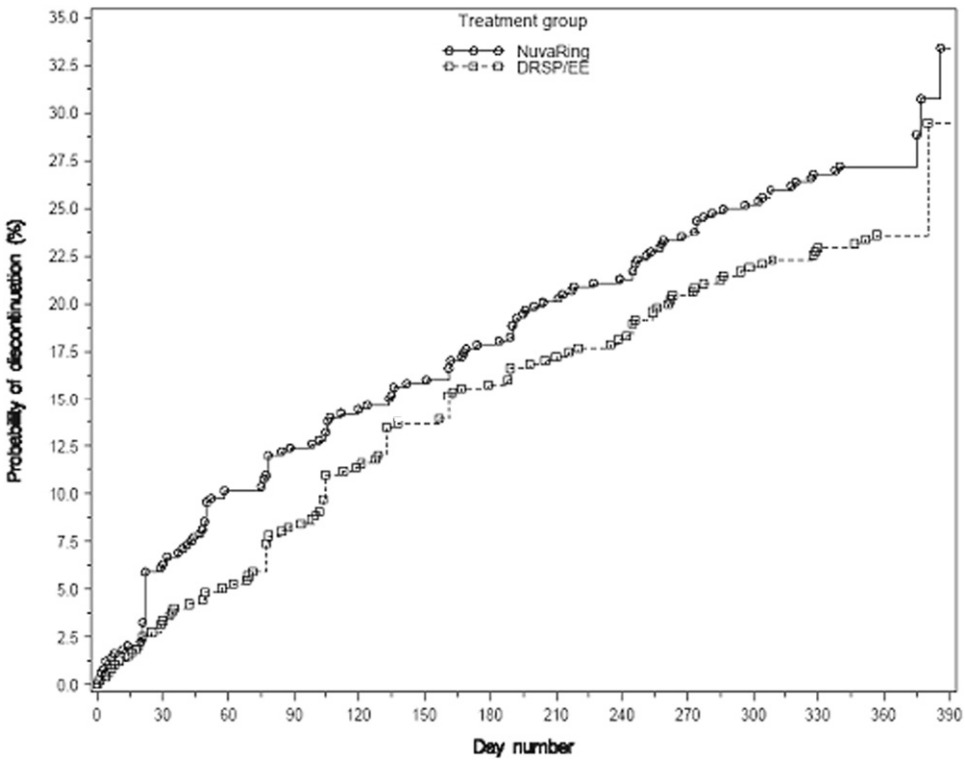

Fig. 2. The cumulative probability of discontinuation due to any reason in subjects receiving NuvaRing or the COC (drospirenone/EE).

Table 1
Baseline demographic and clinical characteristics for the NuvaRing and COC treatment groups (ITT population)

	NuvaRing (n=499)	COC (n=484)
Age [mean±S.D. (years)]	26.6±6.1	26.6±6.2
Race [n (%) Caucasian]	488 (97.8)	476 (98.3)
Weight [mean±S.D. (kg)]	62.4±8.4	62.7±8.1
Body mass index [mean±S.D. (kg/m^2)]	22.4±2.6	22.5±2.6
Nulligravid (%)	306 (61.3)	297 (61.4)
Nulliparous (%)	345 (69.1)	334 (69.0)
Usual duration of menstrual flow [mean±S.D. (days)]	4.7±1.2	4.8±1.2

exposure and Pearl Indices for the ITT and PP populations can be seen in Table 2. The between-group differences in Pearl Indices were not statistically significant.

3.2.1. Compliance

Regimen compliance was high in both groups. For NuvaRing, 89.2% of ITT cycles were fully compliant compared with 85.5% of the COC ITT cycles. For the NuvaRing group, 4.9% of the ring-free periods extended beyond the allowed margin of 24 h (3.6% for >24-48 h and 1.3% for >48 h). Furthermore, over the course of all cycles, approximately 5% of subjects removed the ring temporarily for up to a maximum of 5 h per cycle. For the COC group, >75% of subjects were compliant with their pill regimen during the 21-day pill periods, and >95% of subjects never took a pill during the pill-free period.

3.2.2. Acceptability

Satisfaction with the method during use was high in both groups. In total, 84% of the subjects in the NuvaRing group were satisfied/very satisfied with the ring, and most women (87%) would (absolutely/most probably) recommend the ring to others. In the COC group, 87% of the subjects were satisfied/very satisfied with the pill, and 92% of the subjects would (absolutely/most probably) recommend the COC to others.

Questions regarding ease of use showed that the vast majority of women rarely or never had a problem with insertion (96%) or removal (97%) of NuvaRing during the trial. Temporary ring removal rarely occurred, and most subjects and partners rarely felt the ring during intercourse. Moreover, the majority of partners did not mind that the subject was using the ring. For most of the subjects in the COC group, it was not difficult to take a pill everyday, and the majority of the partners did not mind that the subject was using the COC.

When asked to consider the best contraceptive method, the majority of subjects in the NuvaRing group (66.9%) considered the ring the best method. The main reasons for preference for the ring were "do not have to remember anything" and "easy to use." The majority of subjects in the COC group (76.3%) considered oral contraceptives the best contraceptive method. The main reasons for preference for the pill were "easy to use," "considered an effective method" and "good cycle control."

Table 2
Contraceptive exposure and Pearl Indices for NuvaRing and COC treatment groups

	Exposure (woman-years)	Pearl Index (95% CI)
ITT		
NuvaRing (n=499)	408.8	0.245 (0.006, 1.363)
COC (n=484)	404.8	0.988 (0.269, 2.530)
PP		
NuvaRing (n=450)	318.2	0.314 (0.008, 1.751)
COC (n=450)	364.7	0.548 (0.066, 1.981)

3.3. Tolerability

In general, both NuvaRing and the COC were well tolerated. Treatment groups were comparable regarding the overall incidence of adverse events (NuvaRing: 65.3% of subjects; COC: 63.3%). Slightly more subjects in the NuvaRing group had an adverse event considered to be at least possibly related to study treatment (NuvaRing: 29.1%; COC: 23.5%). The most common adverse events are summarized in Table 3. Headache was the most common event in both groups; upper respiratory tract infection, pharyngitis and influenza-like symptoms were also common but were not considered to be treatment-related. Vaginitis, ring-related events and leukorrhea were more common with NuvaRing, while nausea and breast pain were more common with the COC.

In total, six subjects (1.2%) in the NuvaRing group and 10 (2.1%) in the COC group reported at least one serious adverse event. Three serious adverse events (NuvaRing n=1; COC n=2) were considered to be at least possibly related to the study drug: abdominal pain and cholelithiasis with the COC and deep venous thrombosis with NuvaRing. Genetic testing of the subject with deep venous thrombosis revealed heterozygosity for factor V Leiden and for the

Table 3
Incidence of adverse events (occurring in ≥4% of subjects in either treatment arm)

	NuvaRing		COC	
	Total	Related to study medication[a]	Total	Related to study medication[a]
Headache	87 (17.4)	34 (6.8)	89 (18.4)	37 (7.6)
Upper respiratory tract infection	63 (12.6)	0 (0)	49 (10.1)	0 (0)
Vaginitis	61 (12.2)	23 (4.6)	33 (6.8)	10 (2.1)
Method-related events	35 (7.0)	33 (6.6)	2 (0.4)	2 (0.4)
Pharyngitis	35 (7.0)	0 (0)	28 (5.8)	0 (0)
Leukorrhea	24 (4.8)	16 (3.2)	8 (1.6)	5 (1.0)
Influenza-like symptoms	23 (4.6)	0 (0)	27 (5.6)	0 (0)
Breast pain	17 (3.4)	16 (3.2)	25 (5.2)	23 (4.7)
Nausea	14 (2.8)	4 (0.8)	28 (5.8)	18 (3.7)

[a] Considered to be definitely, probably or possibly related to study drug by the investigator.

prothrombin gene mutation; other identified possible risk factors for the development of venous thromboembolic events included smoking and a recent air journey.

No apparent differences in the overall discontinuation rates due to adverse events were observed between treatment groups: 61 subjects (12.2%) in the NuvaRing group and 48 subjects (9.9%) in the COC group discontinued because of an adverse event. The majority of these events were considered to be at least possibly related to study medication. The most frequent events leading to discontinuation in the NuvaRing group were ring-related events ($n=15$) and headache ($n=5$) and, in the COC group, headache ($n=8$), breast pain ($n=7$) and nausea ($n=6$).

Physical examinations and cervical cytology revealed only very few pathological abnormalities, and there were no apparent differences between the treatment groups. Clinically relevant changes in cervical cytology from screening to the last visit occurred in only a small number of subjects. Two subjects in each group experienced a shift from normal cytology to mild dysplasia: one subject in the NuvaRing group experienced a shift from normal to moderate dysplasia, and one subject in the COC group experienced a shift from normal to carcinoma in situ and was referred to a gynecologist for further investigations.

There were also no clinically relevant or statistically significant differences between treatment groups in changes from baseline for diastolic and systolic blood pressure. The effects of treatment on body weight and body composition are described in a separate article.

4. Discussion

The results of this multicenter, open-label, randomized, phase III trial demonstrate that NuvaRing is as effective, well tolerated and as well accepted as a COC containing 30 μg of EE and 3 mg of drospirenone.

Fewer in-treatment pregnancies occurred with NuvaRing than with the COC, with one pregnancy reported with NuvaRing, compared with four in the COC group. However, although the Pearl Index for NuvaRing of 0.25 in the current study was markedly lower than that of the COC (0.99), this difference was not statistically significant. The contraceptive efficacy of NuvaRing has recently been compared with that of another COC that delivers EE 30 μg/levonorgestrel 150 μg daily [8]. This provides an opportunity to combine the pregnancy data from that trial with the data from the present study, thereby increasing the number of subjects treated with NuvaRing to 1011 and constituting a total exposure of 816.7 women-years. In this pooled NuvaRing group, there were six in-treatment pregnancies, giving a combined Pearl Index estimate for NuvaRing of 0.735 (95% CI: 0.270, 1.599) [10]. In comparison, the Pearl Indices for the COCs were 0.988 for the EE 30 μg/drospirenone 3 mg group ($n=484$) and 1.194 for the EE 30 μg/levonorgestrel 150 μg group ($n=518$) [8]. This shows that the contraceptive efficacy of NuvaRing is comparable with that of the two COCs with which it was compared.

To maintain contraceptive efficacy, compliance with a given method is vital. In the current study, most women were compliant with both ring and pill regimens (89% of NuvaRing cycles were fully compliant vs. 86% of COC cycles). These rates were similar to those reported in a recent study that compared the ring with a COC delivering 30 μg of EE and 150 μg of levonorgestrel and showed compliance rates of around 87% for both NuvaRing and the COC [8]. The similarity in compliance rates between the groups is perhaps surprising, considering that comparisons of COCs with contraceptives that require less frequent dosing, such as the patch, have indicated lower relative compliance rates for COCs [11,12]. Here, it should be noted that comparison of compliance rates in the present study is complicated by the different definitions of compliance used for the two groups. Moreover, being involved in a clinical trial would be expected to lead to subjects having a greater awareness of medication intake and, thus, being less likely to miss doses than in normal daily life. It would be reasonable to expect that this increased compliance would have affected the COC group mostly because of its once-daily dosing, and this may have contributed to the lack of difference between the two groups.

User acceptability is important to the success of a contraceptive method. As NuvaRing is a vaginal method of contraception, practical considerations regarding ease of use are important factors affecting user acceptability. In our study, the user acceptability questionnaire showed that the majority of subjects did not have any problems with the use of NuvaRing (insertion, removal, interference with intercourse) or the COC (intake). The great majority of subjects in each group were also satisfied/very satisfied with the contraceptive method that they used during the trial and were likely to recommend this contraceptive method to others.

It is interesting to note that approximately 50% of subjects in both the COC and NuvaRing study groups were previously using a COC containing 30 μg (or above) of EE before the study start and that two thirds of subjects in both groups were satisfied/very satisfied with their previous contraceptive method (EE/drospirenone 66%, NuvaRing 63%). This means that at the start of the study, most subjects in the NuvaRing group were very satisfied with the method of contraception that they had been using previously, but by the end of the study, these subjects had become very satisfied with NuvaRing. Thus, the current results once again confirm the high user acceptability previously reported with NuvaRing in large 1-year clinical studies [6,7,13].

The tolerability of a contraceptive method also influences its overall acceptability. In our study, both NuvaRing and the COC were well tolerated. The tolerability profile of NuvaRing was similar to that previously reported in other studies [6–8]. Hormonal contraceptives are commonly associated with adverse effects such as bloating, nausea

and breast tenderness [14], which often lead to early discontinuation of COCs [15]. In our study, while events such as vaginitis, leukorrhea and problems relating to ring use were more frequent with NuvaRing, the incidence of events such as nausea and breast pain, often considered to be related to EE, were lower with NuvaRing than with the COC. Moreover, it is notable that although discontinuation rates due to adverse events were similar between the two groups, events relating to ring use were the most frequent reason for discontinuations with NuvaRing (15/61 discontinuations due to adverse events). In contrast, estrogen-related events (breast pain and nausea) were the most frequent reasons for discontinuation in the COC group (13/48 discontinuations due to adverse events).

It was also noticed that discontinuations due to adverse events occurred more frequently in the first few months of the study in the NuvaRing group, compared with the COC group which tended to have a more evenly distributed rate throughout the study. This can be explained by users deciding on the suitability of the NuvaRing method early in the treatment course and the fact that most discontinuations in the NuvaRing group were due to ring-related events. A higher discontinuation rate for NuvaRing in the first few months has been noted previously [6–8]. In addition, since the majority of subjects in both groups had been using a COC prior to the study, the high levels of satisfaction with the previous contraceptive method raises the possibility that for the COC group, compliance could be overestimated and the discontinuation rate underestimated.

In conclusion, NuvaRing had comparable contraceptive efficacy to a COC containing 30 μg EE and 3 mg drospirenone. NuvaRing was also highly acceptable to users and had a tolerability profile similar to that of the COC. Ring-related adverse events were more common with NuvaRing, whereas estrogen-related adverse events were more common in women receiving the COC.

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